Gene expression patterns of human colon tops and basal crypts and BMP antagonists as intestinal stem cell niche factors.

Journal: Proc Natl Acad Sci U S A

Publication Year: 2007

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PubMed link: 17881565

Funding Grants: Training Grant I

Public Summary:

Scientific Abstract:
Human colonic epithelial cell renewal, proliferation, and differentiation are stringently controlled by numerous regulatory pathways. To identify genetic programs of human colonic epithelial cell differentiation in vivo as well as candidate marker genes that define colonic epithelial stem/progenitor cells and the stem cell niche, we applied gene expression analysis of normal human colon tops and basal crypts by using expression microarrays with 30,000 genes. Nine hundred and sixty-nine cDNA clones were found to be differentially expressed between human colon crypts and tops. Pathway analysis revealed the differential expression of genes involved in cell cycle maintenance and apoptosis, as well as genes in bone morphogenetic protein (BMP), Notch, Wnt, EPH, and MYC signaling pathways. BMP antagonists gremlin 1, gremlin 2, and chordin-like 1 were found to be expressed by colon crypts. In situ hybridization and RT-PCR confirmed that these BMP antagonists are expressed by intestinal cryptal myofibroblasts and smooth muscle cells at the colon crypt. In vitro analysis demonstrated that gremlin 1 partially inhibits Caco-2 cell differentiation upon confluence and activates Wnt signaling in normal rat intestinal epithelial cells. Collectively, the expression data set provides a comprehensive picture of human colonic epithelial cell differentiation. Our study also suggests that BMP antagonists are candidate signaling components that make up the intestinal epithelial stem cell niche.

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